NIH RELAIS Document Delivery

NIH-10096741

NIH -- W1 AC7981

PAMELA GEHRON ROBEY
CSDB/NIDR/NIH Bldng 30 Rm 228
30 CONVENT DRIVE MSC 4320
BETHESDA, MD 20892

ATTN:
PHONE: 301-496-4563
FAX: 301-402-0824
E-MAIL:

SUBMITTED: 2001-12-21 15:26:44
PRINTED: 2001-12-27 12:09:52
REQUEST NO.: NIH-10096741
SENT VIA: LOAN DOC
5363472

NIH Fiche to Paper Journal

TITLE:	ACTA ENDOCRINOLOGICA. SUPPLEMENTUM
PUBLISHER/PLACE:	Periodica Copenhagen
VOLUME/ISSUE/PAGES:	1986;279():207-17 207-17
DATE:	1986
AUTHOR OF ARTICLE:	Mauras N; Blizzard RM
TITLE OF ARTICLE:	The McCune-Albright syndrome.
ISSN:	0300-9750
OTHER NOS/LETTERS:	Library reports holding volume or year 0370313 3465162
SOURCE:	PubMed
CALL NUMBER:	W1 AC7981
REQUESTER INFO:	AB424
DELIVERY:	E-mail: probey@DIR.NIDCR.NIH.GOV
REPLY:	Mail:

The McCune-Albright syndrome

KELLY MAURAS, M.D. AND ROBERT M. BLIZZARD, M.D.
Department of Pediatrics University of Virginia School of Medicine
Charlottesville, Virginia, 22901

Abstract. The presence of polyostotic fibrous dysplasia of bone, hyperpigmented skin macules, and precocious sexual development in children is known as the McCune-Albright syndrome. To date, a complex combination of multiple endocrinopathies including goiter, hyperthyroidism, acromegaly, Cushing syndrome, hyperprolactenemia, sexual precocity, hyperparathyroidism, and hypophosphatemic hyperphosphaturic rickets have been described in association with this syndrome. Even though the pathogenetic mechanisms involved in the development of the endocrinopathies is unknown, it was assumed for many years that hypothalamic dysfunction was the cause in most cases. The overwhelming amount of data now permits the development of an alternate hypothesis; one of hyperfunctioning endocrine organs working with relative autonomy from hypothalamic control.

We report a 4 10/12 years old black boy with polyostotic fibrous dysplasia, skin hyperpigmentation, acromegaly, hypercortisolism, hyperthyroidism and premature pubarche. This case represents an excellent example of a common multicellular abnormality in McCune-Albright's. His data and that of others found in an extensive review of the literature prompts us to propose that a derangement in the regulation of the cAMP mediated system is responsible for the endocrinopathies which occur. We postulate the defect may be in all the cells of a specific organ in some instances and in only certain clones in others. Advances in molecular biology research will soon provide us the tools to look at the specific components of the cAMP system in multiple malfunctioning organs and test our hypothesis.

Introduction The systemic and endocrine manifestations of the McCune-Albright syndrome remain one of the most fascinating and challenging problems in pediatric endocrinology. First reported by McCune and Bruch (1937) and shortly thereafter by Albright et al (1937), it comprised the appearance of hyperpigmented macules, precocious sexual development, and bone fractures in young children without any evidence of systemic disease. It was Albright (1947) who first separated the characteristics of these children from other entities such as neurofibromatosis and hyperparathyroidism, and offered the first ideas about pathogenesis. He postulated a centrally mediated mechanism with increased pituitary production of gonadotropins as the cause of the sexual precocity and proposed the theory of pressure at the base of the brain, by expanding bone lesions, as the cause of hypothalamic dysfunction. Today, almost 50 years after the original reports, we remain largely ignorant of the basic pathogenetic mechanisms that operate in these individuals. We now know that this disease presents not only with the classical triad, but often with a multiplicity of dysfunctioning endocrine glands.

In this manuscript we focus on the endocrine manifestations of this disease, as they occur in children and adolescents and explore new areas of possible pathophysiologic mechanisms for the endocrinopathies.

Case Report T., a black male first presented at 2 6/12 years of age with a fracture of his right tibia. At the time, chemical findings of hyperthyroidism were present (see table), as was a palpable goiter on physical exam. The antithyroid antibodies were negative. Propylthiouracil, 50 mg tid, was used to adequately control his hyperthyroid symptoms. When examined at 3 8/12 years he had a large hyperpigmented area with irregular borders covering his left arm, neck, part of the left ear and most of his back and buttocks. His legs were asymmetric with limited hip abduction. X-rays of the long bones, skull, hips, hands and feet showed characteristics of extensive and severe fibrous dysplasia. He was also quite short (fig. 1). Pubic hair, Tanner stage III, was present, but there were no other signs of puberty. His dehydroepiandrosterone sulfate (DHEAS) levels were elevated, compatible with premature adrenarche (table).

A luteinizing hormone releasing hormone (LHRH) test done when 3 8/12 years old showed a prepubertal response (table). At 4 10/12 years of age his testes were 2.5 cm in size, but no further signs of puberty appeared. When blood was drawn overnight (table) his luteinizing hormone (LH) and follicle stimulating hormone (FSH) values remained prepubertal.

Because of his poor growth his cortisol secretion was investigated. When 3 8/12 years old his serum cortisol levels lacked diurnal variation (table). The serum cortisol did not suppress either after a single overnight dose of dexamethasone or after 5 days of low dose followed by high dose dexamethasone (table). A CT scan of the abdomen demonstrated enlarged adrenals with a suggestion of nodular hyperplasia. His adrenocorticotropin hormone was suppressed (<28 pg/ml) when measured twice. After careful consideration of his apparent cortisol excess, poor growth and repeated fractures, bilateral adrenalectomy was performed at 4 4/12 years of age. Subsequently, treatment has been with cortisone acetate and 9 alpha fluoro cortisone. The pathology was that of cortical adrenal hyperplasia. The data obtained six months post operatively is shown in the growth curve (figure 1). A dramatic increase of growth velocity from <4.6 cm/year to 18.8 cm/year occurred post operatively.

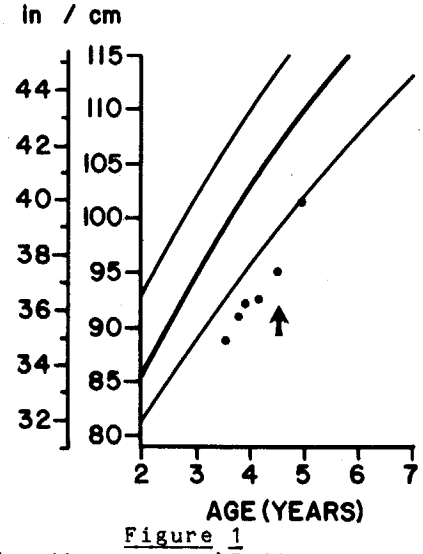

Figure 1
Growth curve. ↑Indicates bilateral adrenalectomy. Lower curve - 5%, middle curve - 50%, upper curve - 95%

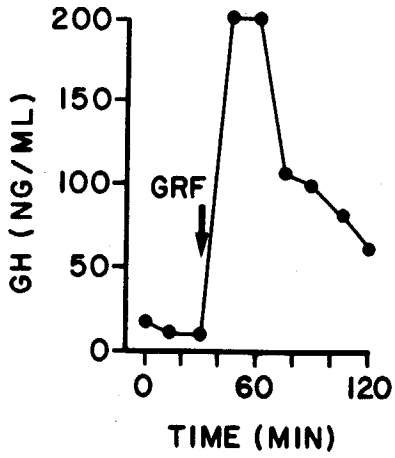

Figure 2
Serum GH response to a 3.3 µg/kg bolus injection of GRF

ented at 2 6/12 years of age
the time, chemical findings
e), as was a palpable goiter
antibodies were negative.
to adequately control his
3 8/12 years he had a large
ers covering his left arm,
his back and buttocks. His
luction. X-rays of the long
showed characteristics of
He was also quite short
was present, but there were
droepiandrosterone sulfate
with premature adrenarche

one (LHRH) test done when 3
ponse (table). At 4 10/12
ze, but no further signs of
awn overnight (table) his
stimulating hormone (FSH)

cortisol secretion was
serum cortisol levels lacked
cortisol did not suppress
examethasone or after 5 days
thasone (table). A CT scan
enals with a suggestion of
opin hormone was suppressed
areful consideration of his
and repeated fractures,
at 4 4/12 years of age.
rtisone acetate and 9 alpha
that of cortical adrenal
s post operatively is shown
amatic increase of growth
occurred post operatively.

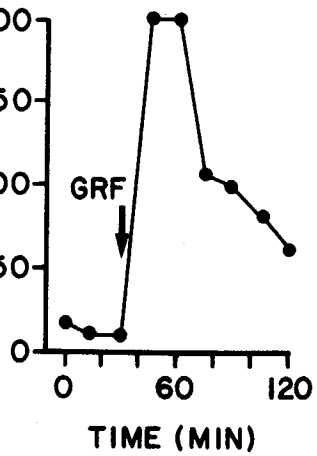

Figure 2
Serum GH response to a 3.3 µg/kg bolus injection of GRF

Coincidentally with his serum cortisol measurements, evaluation of his growth hormone (GH) secretory status was done. At the age of 8/12 years his basal serum GH levels were readily measurable and plasma somatomedin-C was increased (table). An oral glucose tolerance test (OGTT) done at that time showed partial GH suppression (table). After adrenalectomy, at the age of 4 10/12 years, the GH levels were elevated when blood was sampled during the night (table). At the time, his response to a 3.3 ug/kg bolus injection of growth hormone releasing factor (GRF) was exaggerated, typical of patients with acromegaly (figure 2). His OGTT post adrenalectomy showed only partial GH suppression (table). A head CT scan showed no abnormalities of the pituitary. It is probable that his excellent postoperative growth is due not only to the removal of excess cortisol, but to the action of excess GH. His acromegaly has not required therapy so far.

His bone age has remained advanced throughout the course of his disease (7 years at the chronological age 3 8/12 years). This is despite cortisol excess and no evidence of increased sex steroids. It is possible that his advanced skeletal maturation may be due to the period of unrecognized hyperthyroidism.

TABLE: LABORATORY VALUES

Age (yrs)	T4 (µg/dl)	TSH (µIU/ml)	Cortisol (µg/dl)	DHEAS (µg/dl)	Δ4 (ng/dl)	T (ng/ml)	Sm-C (u/ml)	GH (ng/ml)	LH (mIU/ml)	FSH (mIU/ml)
6/12	18.7	1.5					2.8			
8/12	15.9	1.0	12 (am)	204	134	50	5.8	10.6 (d)	4.7 (e)	3.8 (e)
			14 (pm)					5.4	7.3	4.6
			16 (am) (a)							
			18 (am) (b)	346 (b)	116 (b)					
			11 (am) (c)	186 (c)	63 (c)					
3/12	11.3		17 (2pm)	87		50	6.4			
4/12	*									
10/12	9.1	1.0		12		25	3.9	33 (f)	1.6 (f)	3.2 (f)
								38.4 (d)		
								5.1		

Δ4 = Androstenedione T = Testosterone Sm-C = Somatomedin-C

AM: 0800h
PM: 2000h
(a) After single dose of dexamethasone overnight
(b) After low dose of dexamethasone suppression (1.25 mg/100#q.d.)
(c) After high dose of dexamethasone suppression (3.75 mg/100#q.d.)
(d) Before and after an OGTT
(e) Basal and peak response after 2.5 µg/kg LHRH bolus injection
(f) Mean values from 13 samples drawn every 20 min from 2200-0200h
* Surgery performed

Discussion The McCune-Albright syndrome is not familial and chromosomal abnormalities have not been reported. This is in contrast with individuals with the more common form of polyostotic fibrous dysplasia (POFD) not associated with McCune-Albright's, where several family members have been affected (Reitzik and Lownie, 1975).

A pair of monozygotic twins was reported. One developed POFD and sexual precocity, and the other had only mild bone abnormalities (Lemli L, 1977). This is the only suggestion of possible genetic transmission.

Of all the endocrine manifestations of this syndrome, sexual precocity is by far the most common and most carefully studied. Both the syndrome and the sexual precocity are more commonly seen in girls, but boys have been reported as well (Benedict P, 1966; Lightner et al, 1975; Giovanelli et al, 1978). Menses frequently precede any other sign of puberty by several years, arguing against a "normal" pubertal process. In many girls the sexual precocity presents prior to the occurrence of bone lesions, by as long as 9 years. Any girl with early onset of menses prior to or shortly after breast development should be observed for the development of bone lesions and long bone X-rays obtained (Benedict P, 1962; Grant and Martinez, 1983).

In three of ten girls in Benedict's series (1962), and in three of eight girls in Reith et al series (1984), sexual precocity and POFD presented without any evidence of skin lesions, although some patients developed them later.

At both autopsy and examination of surgical specimens, girls with McCune-Albright syndrome lack evidence of ovulation (Benedict P, 1962). Most of the earlier reports that postulated a centrally mediated mechanism as the cause of the sexual precocity did not document adequately the gonadotropin secretory status. In reports where LH and FSH levels were reported, they were not increased in children with sexual precocity and the McCune-Albright syndrome (Benedict P, 1962; Benedict P, 1966; Danon et al, 1975; Tanaka and Suwa, 1977; D'Armiento et al, 1983). Because gonadotropin secretion is so variable and pulsatile in nature, it was not until recently that studies of the gonadotropin pulsatility have been reported in these children. Foster and Comite (1984) demonstrated a lack of gonadotropin pulses, as well as prepubertal LH and FSH responses to exogenous LHRH in five of six girls with McCune-Albright syndrome. Serum was sampled every 20 minutes from 2200-0200h and from 1000-1400h. One girl had normal pubertal pulses for LH and FSH, and pubertal responses to exogenous LHRH, but she also had the most advanced bone age (13.5 years) which may indicate the onset of normal puberty. These authors postulate a gonadotropin independent mechanism, possibly originating in the ovary as the cause of the sexual precocity. This process apparently does not prevent the development of normal puberty at its proper time. Such normal development at adolescence helps explain why patients with the McCune-Albright syndrome eventually may have normal reproductive function (Albright F, 1947; Benedict P, 1962; Carr et al, 1979). Some of these girls have ovarian cysts that enlarge in size in a quasi cyclical fashion with the appearance of menses (Benedict P, 1962; Danon et al, 1975; Reith et al, 1984).

In boys where testicular tissue was available for study the presence of mature Leydig cells and/or increase in tubular size and spermatogenesis led authors to postulate a central hypothalamic mechanism as a cause for the sexual precocity (Benedict P, 1966; Lightner et al, 1975' Giovanelli, 1978). Boys with the syndrome of gonadotropin independent precocity have similar findings in testicular tissue, (Weirman et al, 1985); so the above mentioned histologic findings should not be taken as a sine qua non of gonadotropin activation.

d. One developed POFD and
ly mild bone abnormalities
estion of possible genetic

s of this syndrome, sexual
ost carefully studied. Both
are more commonly seen in
well (Benedict P, 1966;
1978). Menses frequently
ral years, arguing against a
irls the sexual precocity
e lesions, by as long as 9
es prior to or shortly after
or the development of bone
Benedict P, 1962; Grant and

series (1962), and in three
1984), sexual precocity and
skin lesions, although some

rgical specimens, girls with
of ovulation (Benedict P,
hat postulated a centrally
e sexual precocity did not
retory status. In reports
they were not increased in
e McCune-Albright syndrome
non et al, 1975; Tanaka and
cause gonadotropin secretion
it was not until recently
ility have been reported in
84) demonstrated a lack of
tal LH and FSH responses to
h McCune-Albright syndrome.
from 2200-0200h and from
l pulses for LH and FSH, and
but she also had the most
indicate the onset of normal
a gonadotropin independent
ovary as the cause of the
ently does not prevent the
proper time. Such normal
ain why patients with the
y have normal reproductive
, 1962; Carr et al, 1979).
that enlarge in size in a
ance of menses (Benedict P,
4).

as available for study the
ncrease in tubular size and
ate a central hypothalamic
recocity (Benedict P, 1966;
Boys with the syndrome of
have similar findings in
5); so the above mentioned
ken as a sine qua non of

There is only one instance of a properly documented case of a 4 10/12 years old boy (bone age 6 11/12 years) with sexual precocity and the McCune-Albright syndrome where a pubertal pattern of gonadotropin pulsation is demonstrated by frequent overnight blood sampling (Lightner et al, 1975). This boy was later found to have a large pituitary eosinophilic adenoma (Lightner et al, 1976).

There is currently no uniformly effective therapy for the sexual precocity in these children. Since the mechanism seems to be independent of gonadotropin activation in the majority of patients, treatment with the LHRH-analogue (LHRHa) has not proven effective (Comite et al, 1984; Foster et al, 1984; Weirman et al, 1985); unless the patient's bone age is advanced enough at which time the hypothalamic pituitary axis activates and responds to suppression with the analogue (Foster et al, 1984). Cyproterone acetate, acting by peripheral block of the androgen-estrogen effect, has been reported effective in causing regression of the secondary sexual characteristics in patients with sexual precocity, including one girl with McCune-Albright syndrome (Lorini et al, 1981). Recently Foster et al (1985) reported the successful treatment with testolactone, an aromatase inhibitor, of the sexual precocity in a girl with McCune-Albright syndrome which was unresponsive to LHRHa. Further testing of this drug is necessary to better assess the potential usefulness of testolactone in this condition.

Abnormalities of the thyroid, particularly goiters and hyperthyroidism, are the second most common form of endocrinopathy in the McCune-Albright syndrome. The histologic appearance in goiters ranges from multinodular hyperplasia to colloid goiter and even follicular adenoma (Benedict P, 1962; Hamilton and Maloof, 1973). Basal TSH is low, and the TSH response to TRH is often suppressed in these individuals. Antithyroid antibodies are negative. The mechanism for development of hyperthyroidism is not known, but the gland appears to be functioning autonomously. Therapy is similar to that of any other hyperthyroid patient, namely antithyroid drugs, I-131 or surgery.

GH excess has been increasingly recognized in this syndrome. Twelve well documented cases of GH excess have been reported in the English medical literature. Pituitary tumors were demonstrated in six cases (Scurry et al, 1964; Lightner et al, 1976; Joishy and Morrow, 1976; Chung et al, 1983; Hall et al, 1984; Harris R., 1985), and functional GH excess in the other six (Tanaka and Suwa, 1977; Carr et al, 1979; Lipson and Hsu, 1981; Albin and Wu, 1981; Kovacs et al, 1984). The latter cases retained some hypothalamic control of GH secretion as evidenced by the relative GH suppression with an oral glucose load. The reported pituitary tumors where pathologic specimens are available showed a cromophobe adenoma in one (Joishy and Morrow, 1976) and an eosinophilic adenoma in the other (Lightner et al, 1976).

Because of the facial and orbital distortion with narrowing of the optic canal caused by fibrous dysplasia, great care must be applied not to confuse symptoms of progressive facial assymmetry and decreased visual acuity in a patient with McCune-Albright syndrome with acromegaly. Careful measurement of the GH levels, proper suppression tests and radiographic studies must be done to make or exclude this diagnosis.

Therapy for acromegaly in McCune-Albright syndrome is similar to that in any other child with the disease. Transphenoidal removal of the tumors when feasible, bromocriptine and radiation have all been tried. The recent development of a somatostatin analogue now offers

an exciting new alternative to the therapy of this condition (Lamberts et al, 1985).

A relatively rare condition in McCune-Albright syndrome, hyperprolactinemia has been reported in three patients (Carr et al, 1979; Chung et al, 1983; Kovacs et al, 1984). All also had GH excess, one due to a pituitary tumor (Chung et al, 1983), and one due to mammosomatotroph hyperplasia (Kovacs et al, 1984). The third patient did not have surgery, so there is no pathology available. The fact that puberty and menses continued in these patients despite the high prolactins is further evidence that the sexual precocity is probably independent of gonadotropins. Therapy is aimed at the removal of detected tumors or suppression of prolactin secretion with bromocriptine.

Cortisol excess can present in subtle ways in childhood, many times without the classical physical features of moon facies, striae and obesity. Poor growth is often the first clue towards diagnosis of cortisol excess, as it was in the patient reported here. The dramatic improvement in the growth velocity after adrenalectomy in our patient demonstrates the potent inhibitory effect on linear growth of even modestly increased levels of glucocorticoids. In addition to our patient, three additional cases of Cushing syndrome have been associated with McCune-Albright syndrome. Two patients had nodular adrenal hyperplasia (Aaskog and Tvetaraas, 1968; Danon et al, 1975) and one had an adrenocortical adenoma in one gland and nodular hyperplasia in the other (Benjamin and McRoberts, 1973). Lack of suppression of corticosteroids with dexamethasone and the suppressed ACTH levels indicate an autonomous functional derangement of the adrenal glands. Therapy in young children, in our view, should be bilateral adrenalectomy with subsequent cortisol and mineralocorticoid replacement.

Hyperphosphaturic hypophosphatemic rickets has been reported to occur in patients with the McCune-Albright syndrome (Halversen and Aas, 1961; Ryan et al, 1968; Tanaka and Suwa, 1977; McArthur et al, 1979), and also in patients with only fibrous dysplasia of bone (Dent and Gertner, 1976). Low serum phosphorus levels in the presence of normal serum calcium and increased alkaline phosphatase should prompt further studies to make or exclude this diagnosis. The etiology of this condition in association with the bone lesions is unknown. Tanaka and Suwa (1977) postulated an unusual sensitivity of the kidney to the circulating levels of PTH, whereas McArthur et al (1979) suggested the presence of a circulating phosphaturic substance in these individuals. Standard therapy with oral phosphate supplements and vitamin D are necessary to heal the rickets and improve growth.

Low serum phosphorus and elevated alkaline phosphatase in McCune-Albright's could also represent hyperparathyroidism. High serum calcium and PTH levels would support the diagnosis of hyperparathyroidism, an important diagnosis to exclude from the rickets just described. Though originally thought to be the cause of the bone lesions in patients with McCune-Albright's, documented primary hyperparathyroidism has not been reported as part of the syndrome. Benedict P (1962) reported patients with McCune-Albright's and chief cell hyperplasia of the parathyroid, the significance of which is unknown. Firat and Stutzman (1968) and Ehrig et al (1972) on the other hand reported patients with localized fibrous dysplasia of bone that developed parathyroid adenomas. Surgical resection is indicated in such cases, but removal of the adenoma does not improve the progression of the bone disease.

herapy of this condition

McCune-Albright syndrome, hree patients (Carr et al, 1984). All also had GH g et al, 1983), and one due et al, 1984). The third is no pathology available. d in these patients despite nat the sexual precocity is Therapy is aimed at the of prolactin secretion with

e ways in childhood, many ures of moon facies, striae irst clue towards diagnosis atient reported here. The ity after adrenalectomy in nibitory effect on linear s of glucocorticoids. In cases of Cushing syndrome syndrome. Two patients had etaraas, 1968; Danon et al, na in one gland and nodular McRoberts, 1973). Lack of ethasone and the suppressed tional derangement of the en, in our view, should be sequent cortisol and

ckets has been reported to ht syndrome (Halversen and Suwa, 1977; McArthur et al, ous dysplasia of bone (Dent levels in the presence of e phosphatase should prompt iagnosis. The etiology of bone lesions is unknown. nusual sensitivity of the H, whereas McArthur et al ting phosphaturic substance apy with oral phosphate y to heal the rickets and

alkaline phosphatase in nyperparathyroidism. High support the diagnosis of osis to exclude from the thought to be the cause of ne-Albright's, documented reported as part of the ents with McCune-Albright's yroid, the significance of 68) and Ehrig et al (1972) localized fibrous dysplasia as. Surgical resection is ne adenoma does not improve

The advancement of the skeletal maturation seen in these children usually can be attributed to either the sexual precocity or hyperthyroidism in McCune-Albright syndrome. Even so, there are reported cases of advanced bone age, particularly in boys, without either of the above mentioned conditions (Benedict P, 1962). This finding remains unexplained but is perhaps associated to the primary bone disease. Growth data in children with McCune-Albright's has been infrequently reported and even though individuals with sexual precocity may end up shorter than otherwise expected from their genetic background, the presence of GH excess may have opposite effects. In cases of extensive bone disease it appears that there may be simple failure to grow because of the bone lesions.

Lichtenstein (1933) first coined the term polyostotic fibrous dysplasia to describe the radiographic and histologic appearance of this disease. This is a slowly progressive condition that presents mostly with pathologic fractures in childhood due to minimal trauma, but may remain silent for many years and be identified unexpectedly in X-rays taken for other reasons. Normal bone, undergoing physiological reabsorption, is replaced by an abnormal proliferation of an isoamorphous fibrous tissue of spindle cells and bony trabeculae which are poorly formed (Nager et al, 1982). Radiographically in infancy there are "cyst like" lesions in the cortex and ground glass changes in the expanded cortex (Warrick CK, 1973). Expansion of the foci of dysplasia leads to absorption of the cortex, specifically within the first decade. Slowly progressive deformities in the lower extremities, tend to occur after weight bearing years. The course of the bone disease can be quite variable, many patients living functional lives with localized foci of disease, while others end up in wheelchairs.

Any bone can be involved with the disease, particularly the femurs, tibias, carpals, and tarsals. Even though Albright originally suggested lack of epiphyseal involvement (Albright et al, 1937), we know the epiphyses are not spared. Leg assymmetry and unilateral bone disease are common. The bone lesions can precede or follow other manifestations of the disease by years. The majority of individuals with fibrous dysplasia of bone do not have other features of the McCune-Albright syndrome. Indeed, 70% of patients with fibrous dysplasia have monostotic disease, 30% polyostotic, and of the latter, less than 3% have the characteristic manifestations of McCune-Albright syndrome (Nager et al, 1982).

A particularly problematic complication of this bone disorder is when orbital dysplasia or hyperostosis at the base of the skull causes narrowing of the optic canal, ophthalmic nerve damage, and visual loss (Moore et al, 1985). There are reports of associated malignancies, particularly osteogenic sarcoma in bones associated with fibrous dysplasia (Johnson et al, 1979; Nager et al, 1982; Hall et al, 1984; Sevel et al, 1984), but interestingly, no cases of associated malignancies have been reported in McCune-Albright syndrome to date. Unfortunately there is currently no effective treatment for the basic bone disease, but it sometimes stops its progression spontaneously after the second decade (Nager et al, 1982). Fibrous dysplasia of the orbit is progressive in childhood and is best managed by radical surgery when narrowing of the optic canal impairs vision (Moore et al, 1985).

The hyperpigmented macules in McCune-Albright syndrome are similar to the "cafe au lait" spots of neurofibromatosis. The "split skin" preparations can be helpful in distinguishing the macules in McCune-Albright and neurofibromatosis. In the latter there are giant pigment granules in either the malphigian cells, melanocytes or both;

whereas in McCune-Albright's those granules are not consistently present (Benedict et al, 1968). Even though Albright et al (1937) stated that the "cafe au lait" spots in this syndrome resemble the coast of Maine with its irregular borders, and those of neurofibromatosis the coast of California with its regular border, most would agree that such geographic distinctions can be ambiguous. The distribution of the lesions in McCune-Albright's tends to be on either side of the midline, many times on the same side of the affected bones. The lesions are few in number with irregular borders ranging in color from light brown ("cafe au lait") to dark brown (Benedict et al, 1968). These macules are commonly found but are not invariably present in this condition (Grant and Martinez, 1983; Benedict P, 1962; Reith et al, 1984). Hyperpigmented macules may also develop following other manifestations of this syndrome.

We now know that all the organs involved in the complex forms of endocrinopathies present here; pituitary, thyroid, gonads, parathyroid, adrenals, and kidney are indeed activated by a c-AMP mediated mechanism. An abnormality in either the hormone-receptor complex, the guanine nucleotide regulatory unit, the adenylate cyclase activator system or even the protein kinases generated, by working out of cellular control, could perhaps unify the mechanisms of apparent autonomy of many endocrine organs. A logical explanation would be the occurrence of autonomously functioning cells in respect to c-AMP production. These cells could be diffuse or localized in any gland. This would explain the hyperplasia which is found in some hyperfunctioning glands and the nodularity found in other instances. Unfortunately, this hypothesis does not explain the bone or skin lesions in the light of current knowledge. However, refinements in the area of molecular biology will soon allow us to explore various possibilities.

Summary The McCune-Albright syndrome represents a heterogeneous group of patients whose common denominator is the presence of POFD with either cutaneous pigmentation and/or any of a number of endocrinopathies. The proposed theory of a primary hypothalamic dysfunction causing stimulation of many endocrine organs (Albright et al, 1937; Hall and Warrick, 1972) is today less compelling in view of the well documented autonomy of the involved endocrine glands. DiGeorge (1975) observed the similarity of this condition with the syndromes of multiple adenomatosis where end organs undergo neoplastic transformation. We propose a basic abnormality in the cAMP regulation of the endocrine glands that, if confirmed in molecular biology studies, could provide a basic pathophysiologic mechanism causing the multiple dysfunctioning endocrine glands in the McCune-Albright syndrome.

Acknowledgement This work was supported by Clinical Research Center Grant #RR00847.

References

Aarskog D & Tvetaraas E (1968): McCune-Albright's syndrome following adrenalectomy for Cushing's syndrome in infancy. J Pediatr 73:89-96.

Albin J & Wu R (1981): Abnormal hypothalamic-pituitary function in polyostotic fibrous dysplasia. Clinical Endocrinol 14:435-443.

Albright F, Butler AM, Hampton AO, & Smith P (1937): Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females. N Engl J Med 216:727-746.

Albright F (1947): Polyostotic fibrous dysplasia: A defense of the entity. J Clin Endocrinol 7:307-324.

ules are not consistently
ough Albright et al (1937)
this syndrome resemble the
borders, and those of
with its regular border,
tinctions can be ambiguous.
-Albright's tends to be on
on the same side of the
mber with irregular borders
e au lait") to dark brown
commonly found but are not
Grant and Martinez, 1983;
Hyperpigmented macules may
s of this syndrome.

ved in the complex forms of
itary, thyroid, gonads,
deed activated by a c-AMP
ither the hormone-receptor
tory unit, the adenylate
tein kinases generated, by
rhaps unify the mechanisms
ans. A logical explanation
unctioning cells in respect
be diffuse or localized in
asia which is found in some
found in other instances.
explain the bone or skin
. However, refinements in
llow us to explore various

represents a heterogeneous
or is the presence of POFD
/or any of a number of
of a primary hypothalamic
docrine organs (Albright et
less compelling in view of
nvolved endocrine glands.
of this condition with the
nere end organs undergo
basic abnormality in the
ds that, if confirmed in
a basic pathophysiologic
ing endocrine glands in the

by Clinical Research Center

bright's syndrome following
e in infancy. J Pediatr

lamic-pituitary function in
al Endocrinol 14:435-443.
Smith P (1937): Syndrome
disseminata, areas of
n, with precocious puberty

ysplasia: A defense of the

Benedict P (1962): Endocrine features in Albright's syndrome (fibrous dysplasia of bone). Metab 11:30-45.

Benedict P (1966): Sex precocity and polyostotic fibrous dysplasia. Am J Dis Chil 3:426-429.

Benedict P, Szabo G, Fitzpatrick TB, & Sinesi SJ (1968): Melanotic macules in Albright's syndrome and in neurofibromatosis. JAMA 205:618-626.

Benjamin DR, & McRoberts JW (1973): Polyostotic fibrous dysplasia associated with Cushing syndrome. Arch Pathol 96:175-178.

Carr D, Mathie JK, & Mahners AR (1979): Hyperprolactenemia in a patient with the McCune-Albright syndrome. Br J Obst Gynecol 86:330-331.

Chung KF, Alaghband-Zadeh J, & Guz A (1983): Acromegaly and hyperprolactenemia in McCune-Albright syndrome. Am J Dis Child 137:134-136.

Comite F, Shawker TH, Pescovitz OH, Loriaux DL, & Cutler GB (1984): Cyclical ovarian function resistant to treatment with an analogue of luteinizing hormone releasing hormone in McCune-Albright syndrome. N Engl J Med 311:1032-1036.

Danon M, Robboy SJ, Kim S, Sally R. & Crawford JD (1975): Cushing syndrome, sexual precocity, and polyostotic fibrous dysplasia (Albright syndrome) in infancy. J Pediat 87:917-921.

D'Armiento M, Reda G, Camagna A, & Tardella L (1983): McCune-Albright syndrome: Evidence for autonomous multiendocrine hyperfunction. J Pediat 102:584-586.

Dent CE & Gertner JM (1975): Hypophosphatemic osteomalacia in fibrous dysplasia. Q J Med 179:411-420.

DiGeorge A (1975): Albright syndrome: Is it coming of age? J Pediat 87:1018-1020.

Ehrig U & Wilson D (1972): Fibrous dysplasia of bone and primary hyperparathyroidism. Ann Int Med 77:234-238.

Firat D & Stutzman L (1968): Fibrous dysplasia of bone. Am J Med 44:421-429.

Foster CM, Levine-Ross J, Shawker T, Pescovitz OH, Loriaux DL, Curler GB, & Comite F (1984): Absence of pubertal gonadotropin secretion in girls with McCune-Albright syndrome. J Clin Endocrinol Metab 58:1161-1165.

Foster CM, Comite F, Pescovitz OH, Levine-Ross, J, Loriaux DL, & Cutler GB (1984): Variable response to a long-acting agonist of luteinizing hormone-releasing hormone in girls with McCune-Albright syndrome. J Clin Endocrinol Metab 59:801-805.

Foster CM, Pescovitz OH, Comite F, Feuillan P, Shawker T, Loriaux DL, & Cutler GB (1985): Testolactone treatment of precocious puberty in McCune-Albright syndrome. Acta Endocrinogica 109:254-257.

Giovanelli G, Bernasconi S, & Banchini G (1978): McCune-Albright syndrome in a male child: A clinical and endocrinological enigma. J Pediat 92:220-226.

Grant DB & Martinez L (1983): The McCune-Albright syndrome without typical skin pigmentation. Acta Paediatr Scand 72:477-478.

Hall MB, Sclar AG, & Gardner DF (1984): Albright's syndrome with reactivation of fibrous dysplasia secondary to pituitary adenoma and further complicated by osteogenic sarcoma. Oral Surg 57:616-619.

Halvorsen S & Aas Kjell (1961): Renal tubular defects in fibrous dysplasia of the bones. Acta Pediatrica 50:297-303.

Hamilton CR, & Maloof F (1973): Unusual types of hyperthyroidism. Medicine 52:195-215.

Harris RI (1985): Polyostotic fibrous dysplasia with acromegaly. Am J Med 78:539-542.

Johnson CB, Gilbert EF, & Gottlieb LI (1979): Malignant transformation of polyostotic fibrous dysplasia. South Med J 72:353-356.

Joishy SK & Morrow LB (1972): McCune-Albright syndrome associated with a functioning pituitary chromophobe adenoma. J Pediat 89:73-75.

Kovacs K, Horvath E, Thorner MO, & Rogol AD (1984): Mammosomatotroph hyperplasia associated with acromegaly and hyperprolactenemia in a patient with the McCune-Albright syndrome. Virchows Archiv [Pathol anat] 403:77-86.

Lamberts SWJ, Uitterlinden P, Verschoor L, van Dongen KJ, & del Pozo Emilo (1985): Long term treatment of acromegaly with the somatostatin analogue SMS 201-995. N Engl J Med 313:1576-1580.

Lemli L (1977): Fibrous dysplasia of bone. Report of female monozygotic twins with and without the McCune-Albright syndrome. J Pediat 91:947-949.

Lichtenstein L (1938): Polyostotic fibrous dysplasia. AMA Arch Surg 36:874-898.

Lightner ES, Penny R, & Frasier SD (1975): Growth hormone excess and sexual precocity in polyostotic fibrous dysplasia (McCune-Albright syndrome): Evidence for abnormal hypothalamic function. J Pediat 87:922-927.

Lightner ES, Penny R, & Frasier SD (1976): Pituitary adenoma in McCune-Albright syndrome: follow up information (letter). J. Pediat 89:159.

Lipson A & Hsu TH (1981): The Albright syndrome associated with acromegaly: report of a case and review of the literature. Johns Hopk Med J 149:10-14.

Lorini R, Colombo A, Ugazio AG, Salvatoni A, Casternino M, Larieza D, Polito E, Monafo V, Bozzola M, & Severi F (1981): Cyproterone acetate tretment in precocious puberty. J Endocrinol Invest 4:263-270.

McArthur R, Hayles AB, & Lambert PW (1979): Albright's syndrome with rickets. Mayo Clin Proc 54:313-320.

McCune DJ & Bruch H (1937): Osteodystrophia fibrosa. Report of a case in which the condition was combined with precocious puberty, pathologic pigmentation of the skin, and hyperthyroidism, with a review of the literature. Am J Dis Child 54:806-848.

Moore AT, Buncic JR, & Munro IR (1985): Fibrous dysplasia of the orbit in childhood. Clinical features and management. Ophthalmology 92:12-20.

Nager GT, Kennedy DW, & Kopstein E (1982): Fibrous dysplasia: A review of the disease and its manifestations in the temporal bone. Ann-Otol-Rhinol-Laryngol [Suppl] 92:1-52.

Reith KG, Comite F, Shawker TH, & Cutler GB (1984): Pituitary and ovarian abnormalities demonstrated by CT and ultrasound in children with features of the McCune-Albright syndrome. Radiology 153:389-393.

Reitzik M & Lownie JF (1975): Familial polyostotic fibrous dysplasia. Oral Surg 40:769-774.

Ryan WG, Nibbe AF, Schwartz TB & Ray RD (1968): Fibrous dysplasia of bone with vitamin D resistant rickets. A case study. Metab 17:988-998.

Scurry MT, Bicknell JM, & Fajans SS (1964): Polyostotic fibrous dysplasia and acromegaly. Arch Int Med 114:40-45.

Sevel D, James H, Burns R, & Jones KL (1984): McCune-Albright syndrome (fibrous dysplasia) associated with an orbital tumor. Ann Ophtalmol 16:283-297.

Tanaka T & Suwa S (1977): A case of McCune-Albright syndrome with hyperthyroidism and vitamin D resistant rickets. Helv Paediat Acta 32:262-273.

(1979): Malignant
plasia. South Med J

nt syndrome associated
e adenoma. J Pediat

84): Mammosomatotroph
hyperprolactenemia in
ome. Virchows Archiv

Dongen KJ, & del Pozo
acromegaly with the
J Med 313:1576-1580.
. Report of female
une-Albright syndrome.

plasia. AMA Arch Surg

wth hormone excess and
fibrous dysplasia
abnormal hypothalamic

Pituitary adenoma in
mation (letter). J.

drome associated with
the literature. Johns

sternino M, Larieza D,
(1981): Cyproterone
J Endocrinol Invest

bright's syndrome with

fibrosa. Report of a
th precocious puberty,
yperthyroidism, with a
4:806-848.
rous dysplasia of the
res and management.

Fibrous dysplasia: A
ions in the temporal
1-52.
1984): Pituitary and
T and ultrasound in
ne-Albright syndrome.

polyostotic fibrous

Fibrous dysplasia of
A case study. Metab

Polyostotic fibrous
:40-45.
4): McCune-Albright
ith an orbital tumor.

Albright syndrome with
ickets. Helv Paediat

Warrick CK (1973): Some aspects of polyostotic fibrous dysplasia: possible hypothesis to account for the associated endocrinological changes. Clin Radiol 24:125-138.

Wierman ME, Beardsworth DE, Mansfield J, Badger TM, Crawford TD, Crigler JF, Bode HH, Loughlin JS, Kushner DC, Scully RE, Hoffman WH, & Crowley WF (1985): Puberty without gonadotropins. A unique mechanism of sexual development. N Engl J Med 312:65-72.